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Malaria vaccine-is it still required? Are vaccine alternatives enough to achieve malaria control?

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ABSTRACT

Despite ongoing continuous research towards developing a malaria vaccine, we have still not achieved this target and the malaria parasite continues to kill thousands, especially children in developing countries. However, current control methods have had good results in some countries. Can these control methods be enough or should people still keep hoping for a vaccine? Would eradication of malaria be a possibility if no vaccine remains available?

1. Introduction

Extensive efforts to control malaria, supported with increased international funds and political commitment, have led to a significant reduction in the number of malaria cases in the last few years despite the unavailability of a vaccine. The achievements obtained are raising questions about whether a malaria vaccine is still required and whether global eradication of malaria could be a possibility.

1.1. Malaria control

This has been seen even in some highly endemic African countries such as Eritrea, Rwanda and Zanzibar amongst others[1]. Even the burden of malaria in many countries throughout the world had been reduced, there were still 219 million cases of malaria and about 660 000 deaths in African children in 2010[1]. It is believed that vaccines will be a necessary additional tool to the current measures but it is unlikely that they will be effective on their own. Figure 1 illustrates the countries at the risk of malaria and their control status[2].

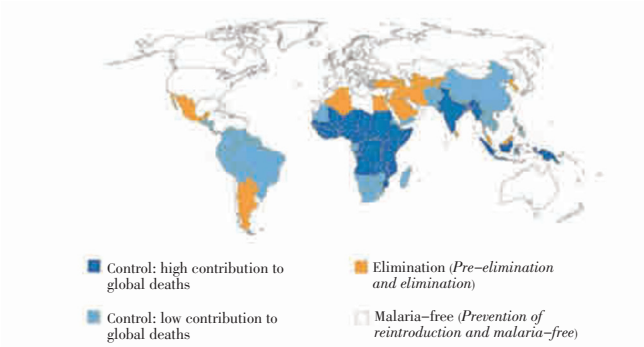

Figure 1. Country categorization by malaria control status and burden[2].

1.2. Malaria vaccines

Malaria vaccines would be useful to both who live in malaria endemic areas and who visit these areas for work, pleasure or missionary purposes. Vaccines have proved efficacious and cost-effective in controlling other diseases such as small pox and whooping cough. An ideal vaccine

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would be one that offers a long-lasting immunity against all variants of each species.

2. Vaccine development

Vaccine developers had been initially challenged to produce a vaccine by 2015 which offers 50% efficacy against severe disease and death from malaria with protection lasting longer than one year. The second goal is to produce a vaccine with 80% efficacy against severe disease by 2025 and it is still rather challenging[3].

Vaccine development has not been easy due to a number of factors including:

1. The complex life cycle of the malaria pathogen with different stage-specific antigens.

2. Antigenic variation of proteins such as the PfEMP-1, which is a parasite protein expressed on the erythrocytes encoded by different var genes. The parasite regularly changes the expression of this var gene so that the infected erythrocyte escapes the recognition by host immunity[4].

3. The complexity of the human immune system and the risks associated with vaccine development.

However, the development of malaria vaccines is still thought to be feasible especially with a better understanding of the human immune process.

Vaccines can be classified in three main groups: pre-erythrocytic vaccines, blood stage vaccines, and transmission blocking vaccines.

2.1. Pre-erythrocytic vaccines

Pre-erythrocytic vaccines are essential to prevent sporozoites infecting beyond the liver stage[5]. These have included studies with the use of irradiated sporozoites, genetically altered parasites as well as the use of surface coat antigens of the parasite such as the circumsporozoite protein. The use of the latter is the most promising and in fact, the RTS,S malaria vaccine is in phase III trials. It is a hybrid molecule consisting of a recombinant antigen from part of the circumsporozoite protein fused to hepatitis B surface antigen and the adjuvant AS01. This large-scale phase III trial showed that the RTS,S malaria vaccine, in infants results in one third less episodes of both clinical and severe malaria, with a good safety profile[6].

2.2. Blood stage vaccines

Blood stage vaccines target the parasite's asexual stages and include the use of surface antigens such as the apical membrane antigen-1 and merozoite surface proteins (MSP1,2,3). To date efficacy has been poor so the possibility of combining the antigens or using a viral vector are being considered[7].

2.3. Sexual stage vaccines

Sexual stage vaccines stimulate antibodies that make the sexual stages of the parasite non-infective to mosquitoes. They would consist of antibodies against the antigens on gametes, ookinites or zygotes when ingested by the mosquito as part of the blood meal and prevent further development of the parasite in the mosquito[8]. Examples include: antigens Pfs25, Pfs48/45 and Pfs230[5]. These vaccines would be ideal in an elimination program and could also be helpful in the elimination of *Plasmodium vivax*[9].

Difficulties encountered in the development of such a vaccine are the fact that antibodies in the blood need to be very high and also the concept of having to vaccinate a very large group of the population has no direct benefit to the individual[7].

RTS,S malaria is likely to succeed in achieving the 50% efficacy goal, yet this level of efficacy does not justify its use alone, but only in combination with other control methods. This is also true because other methods such as insecticide-treated nets help control other vector borne diseases including leishmaniasis and filariasis. A partially effective vaccine would be useful in areas such as parts of Asia and South America where vector control has been difficult due to the different feeding and resting habits of mosquitoes and also where the effective health services are not available[9].

3. Vaccines for elimination

With the concept of malaria elimination back on the cards, the ideal vaccine to be used for elimination purposes would have to be at least 80% effective, should block transmission and would have to be given to the entire population rather than to high risk groups only[10]. Pre-erythrocytic vaccines such as the ones being developed by irradiation of sporozoites or genetic modification could have a role in blocking transmission and also offering some personal protection. Blood stage vaccines, although they decrease the levels and duration of parasitaemia are unlikely to have a major role. A combination of both a pre-erythrocytic vaccine and a transmission blocking vaccine could be an option.

4. Costs and dangers of vaccines

With the development of the most promising vaccine, the RTS,S malaria claims to be about 30%-50% effective. May I query the real need and the cost effectiveness of such a vaccine when the currently available tools alone have been successful in reducing the burden of clinical malaria by 90% in the countries such as Zanzibar[9]. In my opinion, it will probably still be cost-effective in high transmission areas where the clinical burden of malaria is very high but then can such a country use its limited resources to finance a partially-effective vaccine when it can use them for other health programs whilst making use of the other control methods already available?

Possible risks include the development of escape mutants which will not be recognized by the immune mechanisms of vaccinated individuals. This could result in the strains of higher virulence and bring back malaria and high mortality rates[11]. Any method of control including vaccination need to

be sustained and combined with a good surveillance program because once the burden of malaria decreases so does the immunity of the population.

5. Comparing current control methods versus vaccines

5.1. Current methods of control

Studies in Nigeria have shown that strengthening current methods of control will only result in a reduction in parasite prevalence but will not interrupt transmission[12]. I am in agreement with Professor Greenwood who claims that the widespread use of effective treatment and vector control could even lead to a 90% reduction of clinical malaria but it is unlikely that these measures alone will be able to stop the transmission in medium or high transmission areas[9]. In some areas of Asia and Africa, the existing methods of insecticide-treated nets and indoor residual spraying have not been enough to eliminate malaria, probably because of the prevalence of outdoor-resting and outdoor-biting vectors[13].

5.2. Vaccines in addition to current methods of control

In my opinion, vaccines will be a necessary tool applied in conjunction with current and other innovative control measures. The need for a malaria vaccine is felt more in the face of already emerging resistance to the newer drugs such as the artemisinins in some areas of the Cambodia-Thailand border and the pyrethroids in several other countries[14,15].

The malaria vaccine initiative proposes the need from a safe, effective and affordable malaria vaccine to close the gap left by other initiatives[16]. Like many others, I, however, wonder whether the use of some vaccines currently undergoing clinical trials based on development plans made several years ago when the focus was more on decreasing the burden of clinical malaria will be of any use today when we are at a stage where we are even considering elimination in some areas[10].

When considering the need for a vaccine in the control of malaria, one must distinguish between countries with different levels of transmission. World Health Organization defines 3 different stages:

1. Malaria control is reducing the disease burden to a level at which it is no longer a public health problem.

2. Malaria elimination is interrupting local mosquito-borne malaria transmission in a defined geographical area, *i.e.* 0 incidence of locally contracted cases.

3. Malaria eradication is the permanent reduction to 0 of the worldwide incidence of malaria infection caused by a specific agent (*i.e.* a particular malaria species)[13].

6. How can we improve the control methods?

In view of the difficulties with the development of effective and durable vaccines, I believe that alternative approaches to vaccination need to be set up as soon as possible. These would include the correct use of currently available tools to avoid encouraging resistance as well as the introduction of newer control methods[2].

6.1. Vector control

Resistance to current insecticides is on the rise, thus new tools and methods of application as well as newer, active and longer lasting products are essential.

Improvement in the distribution and education on the correct use of long-lasting insecticidal nets and insect repellents can help increase their use.

Following the scaling up of the above methods during the control stages, they will then need to be scaled up and sustained even through the elimination programs.

Broader use of larvicidal applications will be useful in elimination stages but current larviciding methods are not suitable for areas of high malaria transmission because of the large number of breeding sites as well as different vector characteristics.

There is still a deficiency in the tools used against outdoor-biting vectors. The Innovative Vector Control Consortium constantly researches and develops improved products for vector control[17].

6.2. Drugs

The appropriate treatment according to the type of parasites and resistance patterns in the area should be used. Arteminisinin-based combination therapies for *Plasmodium falciparum* and chloroquine and primaquine for *Plasmodium vivax* are the current recommended treatments[18].

The use of monotherapy needs to be completely halted, as well as the sale and availability of sub-standard drugs which potentate resistance and do not result in an effective cure.

There is a strong need for further research and development of drugs and routes which are efficacious encourage patient compliance and have a longer shelf life. The introduction of rectal artesunate for use in remote areas in cases of severe malaria until reaching hospital is showing promising results[19].

New strategies are also required to ensure the delivery of new and cost-effective drugs in the right formulations to the populations mostly at risk including infants, young children and pregnant women[20]. This includes newer drugs for use in intermittent preventive therapy in pregnant women. Research is ongoing with both artemisinin-containing products as well as other combinations such as azithromycin/ chloroquine.

For elimination stages, newer drugs are required that target asymptomatic carriers of hypnozoite stages as well as gametocytes. They should ideally not be limited by side effects such as haemolysis in patients with glucose-6-phosphate dehydrogenase deficiencies.

6.3. Diagnostics

Accurate diagnosis through improved, low cost rapid diagnostic tests with high sensitivity and specificity and good quality assurance are essential especially in areas where diagnosis by microscopy is poor.

Diagnostic tests to identify risk factors such as glucose-

6-phosphate dehydrogenase deficiency prior to the administration of certain drugs can help make the use of certain drugs safer.

Diagnostic methods to identify asymptomatic carriers would be useful in the elimination stages[2].

6.4. Education

An increased awareness of the signs and symptoms of malaria and the seriousness of the condition is essential so they are able to seek the right medical attention promptly without delay.

Awareness of how environmental changes such as deforestation and irrigation projects can create new breeding sites for malaria vectors is important.

An improvement in the surveillance methods is also essential.

6.5. Political commitment and financing

Despite the increase in funds, the finances available remain lower than the resources required to achieve global targets which are estimated to reach >5 billion USD by 2015[1]. An increase in political commitment and funds has been the turning point allowing such an improvement in the control of malaria in several counties in the last five years but these need to be sustained long-term.

7. Conclusion

Malaria is a complex parasitic disease which further perpetuates poverty especially in the countries where it is highly endemic. Despite the successes achieved by some countries using a combination of the current control tools, these will one day become ineffective in the face of an evolving malaria parasite and drug resistance. This is also true because current treatment and control strategies depend on a very small number of compounds. There is a strong need for new innovative methods which should definitely include vaccines. Besides an effective vaccine, other research priorities including new drugs, insecticides and improved surveillance methods are also required if one is to consider the sustained control and the possibly elimination of malaria.

Conflict of interest statement

I declare that I have no conflict of interest.

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